REMARKS

Claims 1, 4-19 and 38-40 are pending.

35 U.S.C. § 103 Rejection

Reconsideration is respectfully requested of the rejection of claims 1, and 4-19 as unpatentable over U.S. Patent No. 6,265,386 (Campbell) in view of U.S. Patent No. 6,110,891 (Pusztai) under 35 U.S.C. § 103(a). Claim 1 is directed to a method for reducing oral mucositis in a human or animal cancer patient undergoing radiation therapy. The method comprises administering to the patient an effective amount of a protective agent selected from the group consisting of D-methionine, L-methionine, a mixture of D-methionine and L-methionine, and a pharmaceutically acceptable salt thereof.

The Campbell '386 reference describes methods for reducing hearing or balance loss, damage to ear cell, weight loss, gastrointestinal toxicity, neurotoxicity, alopecia, and for prolonging survival in patients undergoing treatment with anti-tumor platinum coordination compounds, loop diuretics, aminoglycoside antibiotics, iron chelating agents, quinine, quinidine, or those exposed to toxic levels of noise or radiation. These methods comprise administering an effective amount of a methionine protective agent. However, it is respectfully noted that the Campbell patent makes no mention of mucositis resulting from any type of insult; and that the patent contains not the remotest suggestion that methionine or methionine-like moieties would have any value in dealing with mucositis resulting from radiation exposure or administration of an anti-tumor platinum-coordination compound. As the Office further admits, the Campbell patent makes no mention of oral mucositis resulting from any type of insult; and the patent provides no reason why D-methionine, L-methionine, or D,L-methionine (hereinafter "methionine") would have any value in dealing with oral mucositis resulting from radiation therapy.

Pusztai discloses methods for treating mucosal cell damage caused by various agents comprising administration of lectin. Pusztai does not specifically teach treating oral mucosal cell damage apart from any other type of mucosal cell damage and generally describes nothing more than the state of the art with respect to mucosal cell damage arising from various agents. The Office states that Pusztai "teaches that chemotherapeutic agents and radiotherapy are agents that

damage the mucosal cells"[1] and "it would have been obvious that Campbell's teachings of treating gastrointestinal symptoms in cancer patients would also reduce oral mucositis in a human or animal cancer patient undergoing chemotherapy because it is well known in the art that cancer patients undergoing chemotherapy and radiation are susceptible to destruction of the mucosal cell in the gut (gastrointestinal) and the mouth as evidence by Pusztai."[2]

Contrary to the assertion in the Office action, amended claim 1 requires more than administration of the drug methionine. The limitation of the claim to treatment of patients undergoing radiation therapy is a positive concrete limitation of the claim that cannot be ignored in evaluating obviousness under § 103(a). Since the patient population treated by claim 1 is cancer patients undergoing radiation therapy, the issue is whether it would have been obvious to treat oral mucositis arising from radiation therapy in cancer patients by administration of methionine.

While it is now known that treatment of a patient under chemotherapy with methionine would inherently ameliorate oral mucositis arising from radiation, such inherency was unrecognized in the art, is placed in possession of the art only by the instant application, and thus is not a basis for establishing obviousness under § 103(a). Further, it would not have been inherent that any subject described in the Campbell '386 patent would have suffered from oral mucositis and thus, the Campbell '386 patent would not have made it obvious that administration of methionine would have reduced oral mucositis in a cancer patient in need thereof undergoing radiation therapy as required by claim 1.

Further, there can be no basis for obviousness where the prior art further fails to recognize the potential effect of the treating agent against the condition specified in the claim. As the C.C.P.A has stated in reversing an obviousness rejection of a claim to a method of treating a specified condition with a defined treatment agent based on the inherent effect of treating a different condition with a similar agent.

> [Inherency] is quite immaterial if, as the record establishes here, one of ordinary skill in the art would not appreciate or recognize that inherent result, *in re Shetty*.[3]

The method claims at issue in *Shetty* were directed to methods for appetite control and the cited prior art disclosed compounds and dosages useful for combating microbial infestation. The

[1] *See* Office action dated January 20, 2010 at page 5.
[2] *See id.*
[3] 195 U.S.P.Q. 753.

Shetty court stated that the Office had "failed to show a reasonable expectation, or some predictability" that the prior art compound disclosed in the first reference would be an effective appetite suppressant if administered in the dosage disclosed in the second reference and that the Office's hindsight assertion that the dosages would make the weight loss method obvious was insufficient.[4] Similar to *Shetty*, claim 1 recites a method for reducing oral mucositis in a cancer patient undergoing radiation therapy by administering methionine to said patient while the reference cited against these claims discloses methods for preventing or reducing ototoxicity, methods of preventing or reducing weight loss, methods of preventing or reducing gastrointestinal toxicity, methods of preventing or reducing neurotoxicity, and methods of preventing or reducing alopecia in patients, but only in patients undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound.

Contrary to the Office's assertion that "one skilled in the art would reasonably treat oral mucositis with the same active agent used in treating gastrointestinal toxicity,"[5] oral mucositis and gastrointestinal toxicity are not necessarily coextensive. While oral mucositis is sometimes broadly classified as a form of gastrointestinal toxicity, oral mucositis is an effect distinctly separate from the effects ordinarily contemplated by "gastrointestinal toxicity" such as nausea, diarrhea and abdominal pain, and generally results from different pathological mechanisms. For example, the mocosa is the most highly differentiated layer of the GI tract. The mucosa generally consists of the epithelium, the lamina propria (i.e., the supporting loose connective tissue), the submucosa (i.e., deeper connective tissue that supports the mucosa) and the muscularis mucosae (i.e., thin layer of smooth muscle between the mucosa and submucosa). Tissue specialization and surface shape are correlated with functional differentiation along the tract. For example, in the oral cavity, the epithelium is protective, the lamina propria is unspecialized, and the muscularis mucosae are not present. In contrast in the stomach, the gastric mucosa is specialized for production of digestive acid and enzymes and the mucosal surface of the epithelium consists of mucus-secreting cells for protection against self-digestion. In the small intestine, the intestinal mucosa is specialized for absorption of nutrients and surface area is increased.

[4] See id. at 756.
[5] Office action dated July 9, 2009 at page 4.

Further, a declaration from Dr. James P. Malone[6] is submitted herewith describes the differences between oral mucositis and other types of mucositis in more detail.

Thus, oral mucositis is a subtype entirely different from the subtypes to which the references are principally directed. Further, the material difference between oral mucositis and gastrointestinal toxicity is illustrated by Rappoport et al., of record. Not only are the methods for scoring oral mucositis separate and vastly different from those used for gastrointestinal toxicity, but, even more significantly, the authors *found no association or correlation* between the results of the measures for gastrointestinal toxicity and those for oral mucositis in clinical populations.

The Office action states that oral mucositis is a well known result of chemotherapy and radiotherapy, but there is no suggestion in the references, or otherwise in the art, that treatment effective against gastrointestinal toxicity would be effective against mucosal damage in an entirely different part of the gastrointestinal tract where the mucosal cells are much different. Thus, there was no reason to attempt substitution of the Campbell treatment agent for ameliorating oral mucositis, much less any basis for expectation of success. Nowhere in the art is there any suggestion that the mechanism by which oral mucositis is induced might be the same as for gastrointestinal toxicity, and given the vast differences between these treatments and how they function within patient's system, a skilled medical researcher would not have looked to Campbell as a source of learning for treatment of oral mucositis.

More significantly, even if one skilled in the art were to read Campbell's "gastrointestinal toxicity" as including oral mucositis, Pusztai contains no suggestion that oral mucositis arising from radiation would result from the same pathological mechanism which produces oral mucositis from chemotherapy, much less that any treatment for oral mucositis induced by chemotherapy would or could have any beneficial effect on oral mucositis induced by radiation. Radiation treatment is usually directly targeted to a specific area of the body wherein the diseased tissue is located, whereas chemotherapy operates through more systemic mechanisms. While systemic effects may also be incurred from radiation, mucositis is understood to arise from proximity to diseased tissue. More generally, the pattern of toxicities to tissues from radiation shows that the mechanisms of damage from radiation exposure are different in different tissues and depend on the specific region of exposure to radiation. Thus, since the mechanisms of radiation damage to different tissues are unpredictable, and the mucosal cells in different parts

[6] Dr. Malone is a surgeon employed by Southern Illinois University, the assignee of the instant application.

of the gastrointestinal tract are highly differentiated depending on the function of the tract, there was no reasonable basis for expectation that administration of methionine would be beneficial to ameliorate oral mucositis arising from radiation therapy.

There was no motivation in the art to administer methionine to a cancer patient undergoing radiation therapy and in need of treatment for oral mucositis. Although the side effect of oral mucositis in patients receiving radiation treatments for various conditions was known, the art did not suggest a way to alleviate radiation-induced oral mucositis that was in any way comparable to the instantly claimed method. Thus, there was no teaching, motivation or suggestion in the art to try methionine or any amino acid as a treatment for oral mucositis arising from radiation. Further, there was not a reasonable expectation that administration of methionine to a cancer patient undergoing radiation therapy and in need of treatment for oral mucositis would have had a beneficial effect.

Claims 38-40

Reconsideration is respectfully requested of the rejection of claims 1 and 38-40 as unpatentable over U.S. Patent No. 6,265,386 (Campbell) in view of U.S. Patent No. 6,110,891 (Pusztai) under 35 U.S.C. § 103(a). Claim 38 is dependent on claim 1 and directed to a method of reducing oral mucositis wherein the patient is a cancer patient, is undergoing radiation therapy, and is undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. Thus, claims 38-40 are patentable over U.S. Patent No. 6,265,386 (Campbell) in view of U.S. Patent No. 6,110,891 (Pusztai) under 35 U.S.C. § 103(a) for at least the same reasons as claim 1.

It is respectfully submitted that the Office has failed to establish obviousness based on the cited references or by evidence of the level of skill in the art or the nature of the problem that is not based upon impermissible hindsight reconstruction. Thus, claims 1 and 38-40 are patentable over the cited references.

Obviousness-type Double Patenting

Reconsideration of the rejection of claims 1, 4-19, and 38-40 as being unpatentable over claims 1-9, 11-13, 15-25, and 27-33 of U.S. Application No. 10/694,432 is respectfully requested. The analysis employed in an obvious-type double patenting rejection parallels the

guidelines of a 35 U.S.C. § 103 obviousness determination.[7] However, an important distinction exists. A rejection for obviousness must be based on a comparison of the claimed invention to the entirety of the disclosure in the prior art reference, whereas an obviousness-type double patenting rejection must be grounded on a comparison of the claimed invention to the claims, **and only the claims**, of the reference.[8]

The '432 application contains claims directed to methods for treating alopecia in a patient experiencing exposure to radiation by administering D-methionine, L-methionine, or a mixture of D- and L-methionine. Because the mechanism for alopecia and oral mucositis arising from radiation therapy are significantly different, none of the claims of the '432 application provides a reason to try methionine for treatment of oral mucositis in a cancer patient undergoing radiation therapy. Additionally, all patients exposed to radiation and suffering from alopecia would not have inherently suffered from oral mucositis because the target and dose of radiation exposure would have been important. Also, the '432 claims provide no reason to expect that such administration of D-methionine, L-methionine, or a mixture of D- and L-methionine would have been successful to reduce oral mucositis in a cancer patient undergoing radiation therapy. Thus, like *in re Shetty*, since the Office has provided no reasonable expectation that the administration of methionine would have been successful to reduce oral mucositis in a cancer patient undergoing radiation therapy, claims 1, 4-19, and 38-40 are not obvious in view of the claims of the '432 application.

A. U.S. Patent Nos. 6,187,817 and 7,557,142

Subject claims 1, 4-19, and 38-40 are directed to methods for reducing oral mucositis in a cancer patient undergoing radiation therapy, the method comprising administering to said patient an effective amount of a protective agent comprising monomeric methionine. In contrast, claims 1-28 of the '817 patent are directed to a method for preventing or reducing ototoxicity, claims 29-30 are directed to methods of preventing or reducing weight loss, claims 31-32 are directed to methods of preventing or reducing gastrointestinal toxicity, claims 33-34 are directed to methods of preventing or reducing neurotoxicity, and claims 35-36 are directed to methods of preventing or reducing alopecia wherein all of these conditions arise from treatment with a

[7] In re Braat, 937 F.2d 589 (Fed. Cir. 1991).
[8] Purdue Pharma L.P. v. Boehringer Ingelheim GMbH, 98 F.Supp.2d 362, 392, 55 USPQ2d 1168, 1190 (S.D.N.Y. 2000), *aff'd*, 237 F.3d 1359, 57 USPQ2d 1647 (Fed. Cir. 2001).

chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. Accordingly, because the claims of the '817 patent are not directed to reducing oral mucositis in a cancer patient undergoing radiation therapy, the claims do not include all the elements of subject claims 1 and 3-19. Further, as discussed above in connection with *in re Shetty*, in order to be obvious, the Office must show there would have been some reasonable expectation that methionine would have been effective for reducing oral mucositis in such a patient. The Office has provided no reasonable expectation of success.

Further, claims 1-29 of U.S. Patent No. 7,557,142 are directed to methods of reducing ototoxicity in patients undergoing treatment with an anti-tumor platinum coordination compound by administering L-methionine or a mixture of D- and L-methionine. Like the '817 patent, the claims of the '142 patent are not directed to reducing oral mucositis in a cancer patient undergoing radiation therapy, the claims do not include all the elements of subject claims 1 and 3-19. Further, as discussed above in connection with *in re Shetty*, in order to be obvious, the Office must show there would have been some reasonable expectation that methionine would have been effective for reducing oral mucositis in such a patient. The Office has provided no reasonable expectation of success.

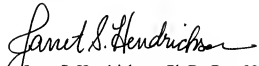
Noting that the '817 patent may be considered a § 102(b) reference, applicant further directs the Examiner's attention to the failure of the '817 specification to have led a person of ordinary skill to the method defined by subject claim 1. In sum, claims 1, 4-19, and 38-40 are not obvious in view of the claims of the '817 or '142 patents.

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,



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